REMARKS

I. Status of the Claims

Claims 1, 2, 4-9, 31, and 75-81 were under consideration. Claims 1, 4-7, 31, and 76-79 have been amended for clarity and Claims 8-9 and 80-81 have been canceled herein. No new matter or new issue is presented in the amendments. Support for the amendments can be found in the current specification, for instance, paragraphs [021], [052], [053], and Example 18 (paragraphs [0211] and [0212]. Reconsideration of the present application and allowance of Claims 1, 2, 4-7, 31 and 75-79 is respectfully requested in view of the following reasons.

II. Objection to the Specification – Title

The Examiner objected that the title of the invention is not descriptive, and requested a new title that is clearly indicative of the invention to which the claims are directed. Applicants respectfully traverse the objection. However, in an effort to advance prosecution, Applicants have deleted the old title and replace it with the new title "Human Aneuploid Embryonic Stem Cell Culture". Applicants believe that the new title is descriptive and clearly indicative of the invention to which the claims are directed.

III. New Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1, 2, 4-9, 31, and 75-81 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner rejected claims 1, 31, and dependent claims thereof, because the term "the cells of the culture" is alleged not clear as to which cell types are actually being claimed that do not express SSEA1, but express other biomarkers as claimed in the claims, the majority cells with the abnormal karyotype, or the remaining cells in the culture.

Applicants respectfully submit that the term "the cells of the culture" is clear and definite, referring to the majority cells with abnormal karyotype. In an effort to advance prosecution, Applicants have amended claims 1 and 31 to explicitly recite "wherein the majority of the cells of the culture do not express SSEA1, express SSEA3, SSEA4, Tra-1-60, Tra-1-801, and express nestin substantially uniformly". Therefore, in view of the amendment, the rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

IV. New Rejections under 35 U.S.C. § 112, first paragraph - New Matter

Claims 1, 2, 4-9, 31 and 75-81 were newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, particularly because the Examiner alleged that the application is silent as to which specific autosomal abnormality corresponds to the specific combination of markers claimed, and silent on establishing a clear nexus between a particular karyotype aneuploidy and the expression pattern of the cell surface markers claimed. Accordingly, the Examiner concluded that at the time of the application was filed, an Artisan of skill would not recognize from the disclosure that applicant was in possession of any of numerous human aneuploid stem cells that regardless of their karyotypic abnormality, express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and nestin, either as an individual cell line or as a majority of cells in a mixed stem cell culture, as claimed. Applicants respectfully traverse the rejection.

In an effort to advance prosecution, Applicants have amended the independent claims 1 and 31 to explicitly recite that the claimed human aneuploid stem cell culture has a majority of cells with a stable abnormal karyotype that comprises a trisomy selected from the narrowed group consisting essentially of sex chromosome X, autosomal chromosome 12, autosomal chromosome 17, and combinations thereof, and wherein the majority of cells of the claimed human aneuploid stem cell culture do not express SSEA1, but do express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80, and nestin. Support for such amendments can be found in the current specification, for instance, paragraphs [021], [052], [053], and Example 19. Accordingly, the instance specification provides a clear nexus between a particular karyotype aneuploidy, *i.e.*,

trisomy of sex chromosome X, and/or autosomal chromosomes 12 and 17, and the expression pattern of the cell surface markers claimed. Therefore, the subject matter claimed in the amended claims 1 and 31 is disclosed in the current specification. Applicants therefore respectfully request that the rejection under 35 U.S.C. §112, first paragraph with respect to the written description/new matter issue be withdrawn.

V. New Rejections under 35 U.S.C. § 112, first paragraph - Scope of Enablement

Claims 1, 2, 4-9 and 31 stand rejected under 35 U.S.C. §112, first paragraph, in modified form, as failing to comply with the enablement requirement for reasons of record. However, the Examiner indicated that in view of the evidence supplied by Applicants on June 9, 2008 (*see* Response to Advisory Action), the claims are enabled for the human aneuploid embryonic stem cell line BG01V derived from human ES cell line BG01, deposited as ATCC No. SCRC-2002.

Nevertheless, the Examiner found that Applicants' arguments that the BG01 cell line is not the only cell line enabled by the current invention, and that the claims are directed generically to methods and cell cultures of human aneuploid embryonic stem cells, persuasive only in part. The Examiner alleged that the claims do not establish a clear nexus between a particular karyotypic aneuploidy and the expression pattern of the cell surface markers claims. Moreover, the Examiner alleged inconsistent results with respect to the expression of certain markers claimed, and certain characterizations of the BG01V cell line.

Applicants respectfully traverse the rejection, and particularly point out that in an effort to advance prosecution, Claims 1 and 31 have been amended to recite a human aneuploid embryonic stem cell culture with a stable abnormal karyotype comprising a narrowed trisomy selected from the group consisting essentially of a sex chromosome X, and autosomal chromosomes 12 and 17, and combinations thereof. As discussed above, the instant specification supports the amendments, *e.g.*, paragraphs [021], [052], [053], and Example 19. Therefore, as suggested, the amended claims are enabled for a stable human aneuploid embryonic stem cell culture, comprising a cell with a stable abnormal karyotype that is selected from trisomies of XXY, +12, +17, or combinations thereof.

Applicants respectfully maintain that one of skill in the art would reasonably expect that more than one combination of the trisomies of sex chromosomes X, autosomal chromosome 12, and autosomal chromosome 17 can result in the useful stable cell lines, e.g., BG01 variant cell line, of the present invention. In view of the present application and other evidence submitted during prosecution, one would expect to routinely create and screen for stable human aneuploid embryonic stem cell cultures having trisomies of X, +12 and/or +17 chromosomes, with a reasonable expectation of the corresponding marker combination.

Moreover, Applicants note that dependent claims 7 and 79 are directed even more specifically to cell lines having a stable abnormal karyotype that comprises a specific trisomy of sex chromosome X, and autosomal chromosomes 12 and 17.

Therefore, for at least the foregoing reasons, the present specification is sufficient to enable one of ordinary skill in the art to make and use the claimed invention without exercising undue experimentation. Therefore, the rejection under 35 U.S.C. §112, first paragraph with respect to the scope of the enablement should be withdrawn.

VI. New Rejections under 35 U.S.C. §102(a)

Claims 1, 2, 4-9, 31 and 75-81 were newly rejected under 35 U.S.C. §102(a) as being anticipated by Draper et al. (Nature Biotech. 22(1):53-54; published online Dec. 7, 2003), as evidenced by Mitalipova et al. (U.S. Patent Publication No.: 2005/0037488; effective filing date Aug. 6, 2001) and Nakayama et al. (U.S. Patent Publication No.: 2005/0221479; effective filing date June 23, 2003). Applicants respectfully traverse the rejection.

According to the Examiner, Draper et al. described the claimed invention, first because Draper et al. teach the recurrent gain of chromosomes 17 and 12 in cultured human embryonic stem cells, wherein the cells retained an undifferentiated phenotype, were positive for SSEA3, Tra-1-60 and Oct4 (*see* pages 7 and 8 of the Office Action). Secondly, the Examiner alleged that Draper et al. also state that aneuploid cells inherently do not express SSEA1 and express SSEA4 and Tra-I-81. Therefore, according to the Examiner, "the burden is on the Applicant to prove

that the claimed products are functionally different than those taught by the prior art and to establish patentable differences (*see* page 9 of the Office Action)".

Contrary to the Examiner's assertions, the below describes in detail that the claimed product, an aneuploid hES cell, is functionally and patentably distinct from that described in Draper et al. and for at least the following reason:

Draper et al. do not describe a stable aneuploid cell line. Draper et al. describe that, with each increasing number of cell passages, the H7 and H14 cell lines have a corresponding sporadic increase in the prevalence of trisomy 12 and/or 17, *e.g.*, 76 to 95%; or a gain of chromosome 12 in a subpopulation of cells (*see* page 1, right column). Draper et al. state that no other consistent karyotypic changes were noted (see page 53, 1st column). Draper et al. also describe various aneuploid cells in Table 1, which cells also had sporadic chromosomal changes (*see* page 53, 2nd column). Table 1 of Draper et al. may describe various aneuploid cells with chromosome changes in chromosomes 12 and/or 17, but it is clear that the chromosome changes in that report were not stable, thus not producing the human aneuploid stem cells with a "stable abnormal karyotype" of the claimed invention. Further, the chromosome stability (or instability) of those cell cultures was not dependent on the passage number since H14 was taken out to 41 passages and the H1.1A and H1.1B were taken out to passage 71.

In contrast to the sporadic chromosomal changes (or chromosomal instability) described in Draper et al., the aneuploid hES cells of the presently claimed invention are chromosomally stable. An example of such cells is demonstrated and reported in Plaia et al. (2006) of record (*see* Exhibit B, Plaia et al., (2006), Characterization of new NIH-registered variant human embryonic cell line: A tool for human embryonic stem cell research, 24:531-5460) (note the common co-author and co-inventor of the present invention, Thomas Schultz). One of the claimed human aneuploid stem cell cultures referred to as BG01V, by Plaia et al, states that "The BG01V hESC line evolved from routine enzymatic passing by BresaGen, Inc., and exhibits a karyotype of 49 chromosomes (XXY, +12, +17). Through 25 passages, this BG01V maintained the karyrotype 49XXY, +12, +17 (*see* page 536, 1st paragraph under Results – Karyotype and Propagation In Vitro).

Additionally, another distinguishing function of the presently claimed cell lines is that "stable variant hESC lines may more closely parallel normal hESC lines (*see* page 532, last sentence of the paragraph bridging pages 531 and 532 of Plaia et al.)". For example, Plaia et al. demonstrate that such a cell line was "easier to manipulate *in vitro* and recover more rapidly after passaging and cryopreservation," relative to their normal parental cell lines (*see* page 532, second paragraph). Plaia et al., also demonstrate that such cells grow, propagate and differentiate similar to the karyotypically normal parent hESC line. Lastly, as proof of the chromosomal stability of such a trisomy variant cell line, Plaia et al., passaged these BG01V cells through 25 passages, and retained the variant karyotype 49XXY, +12, +17 (*see* page 536, Results section, first column). This is in stark contrast to the sporadic chromosome changes of the hESC lines described in Draper et al., above, made by a different process which did not anticipate creating stable cell lines with these advantageous characteristics.

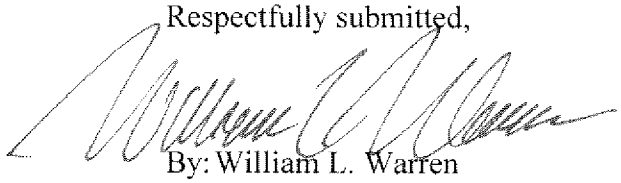
Based on the foregoing, the claimed human aneuploid stem cell culture is functionally and patentably distinct over that of chromosomally sporadic and unstable variant hES cell lines reported in Draper et al. Accordingly, Applicants respectfully request the rejections under 35 U.S.C. §102(a) as being anticipated by Draper et al. should be withdrawn.

VII. Conclusion

Based on the above amendments and remarks herein, all of the pending claims are believed to be in condition for allowance and a notice to that effect is respectfully solicited.

Please charge any additional fees, or credit any overpayment, to Deposit Account 19-5029 (Ref.: 18377-0067). If there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited to call the undersigned attorney at (404) 853-8081.

Respectfully submitted,



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